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Localization of Seizure Onset Area from Intracranial Non-Seizure EEG by Exploiting Locally Enhanced Synchrony

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Abstract— For as many as 30% of epilepsy patients, seizures are poorly controlled with medication alone. For some of these patients surgery may be an option: the brain region responsible for seizure onset may be removed surgically. However, this requires accurate delineation of the seizure onset region. Currently, the key to making this determination is seizure EEG. Therefore, EEG recordings must continue until enough seizures are obtained to determine the onset region; this may take about 5 days to several weeks. In some cases these recordings must be done using invasive electrodes, a procedure that includes substantial risk, discomfort and cost.

In this paper, techniques are developed that use periods of intracranial non-seizure ("rest") EEG to localize epileptogenic networks. Analysis of intracranial EEG (recorded by surface and/or depth electrodes) of 6 epileptic patients shows that certain EEG channels and hence cortical regions are consistently more synchronous ("hypersynchronous") compared to others. It is shown that hypersynchrony seems to strongly correlate with the seizure onset zone; this phenomenon may in the long term allow to determine the seizure onset area(s) from non-seizure EEG, which in turn would enable shorter hospitalizations or even avoidance of semi-chronic implantations all-together.

I. INTRODUCTION

Approximately 50 million people worldwide (2.5 million in the United States alone) have epilepsy. More than 50 percent of those suffer from localization-related epilepsy. Unfortunately, 30% of these patients continue to have seizures despite maximal medical therapy (see, e.g., [1]). Furthermore, many patients suffer from considerable side effects of the medications. On the other hand, regional surgical resection may provide seizure reduction or even cure [2]. However, it is of crucial importance to reliably localize the epileptic brain area(s). At present, one relies mostly on (scalp or intracranial) EEG that contains *seizure* activity ("ictal EEG" or "seizure" EEG) to determine the seizure onset area; since seizures usually do not occur frequently, recordings must last a long time (from several days to several weeks) until sufficient seizures have occurred (typically between 3 and 5).

In this paper, we investigate whether *non-seizure* intracranial EEG can be used to localize epileptic brain tissue. We will show that non-seizure EEG indeed contains much relevant information about the location of epileptic brain

areas. In the long term, one may therefore no longer need to rely on seizure EEG, but instead use short non-seizure EEG recordings to determine the seizure onset area; this would drastically reduce the hospitalization time for intractable-epilepsy patients. Our methodology would be useful for focal epilepsies regardless of underlying etiology. This includes focal epilepsy secondary to cortical dysplasia, tuberous sclerosis, a stroke, tumor, vascular malformation, or trauma.

In order to delineate the seizure onset zone from non-seizure EEG, we will exploit the phenomenon of *locally enhanced EEG synchrony* ("hypersynchrony"). A unifying principle emerging from decades of intense research is that seizures are a property of abnormally firing neurons that, entrained by an imbalance of excitation and inhibition, discharge *synchronously* in a critical ensemble [3]. Moreover, several studies have suggested that multivariate analysis of *seizure-free* (rest) EEG, in which the relationship between different channels of activity are compared, may help to delineate epileptogenic cortex (e.g., [4], [5], [6], [7], [8], [9]).

Most of those studies, however, have examined *scalp* EEG data, only a small number have focused on *intracranial* recordings; the latter studies all consider recordings from intracranial *surface* electrodes. In this paper, we analyze recordings from surface electrodes as well as *depth* electrodes. As we will explain, the recordings from depth electrodes provide us some new insights concerning the problem of localizing seizure onset areas.

Moreover, all existing studies make use of a single synchrony measure, (e.g. mean phase coherence [6], [8] or synchronograms [7]). It is crucial to verify whether hypersynchrony is a true and consistent property of the epileptogenic cortex. To this end, we will compare the outcomes of a large variety of synchrony measures.

This paper is structured as follows. In Section II we describe our EEG data and the pre-processing we carried out. In Section III we describe our results, and in Section IV we briefly discuss a thought-provoking observation. At the end of the paper we offer some conclusions.

II. METHODS

We have analyzed intracranial EEG data from 6 patients with intractable epilepsy: the EEG of 4 patients (Patient 1 to 4) was recorded with both grid and depth electrodes, the EEG of 2 patients (Patient 5 to 6) was recorded with depth electrodes only. In each case, 1-hour segments of data, at least 48 hours separated from seizure activity, were examined. The data was band-pass filtered between 4 and 30Hz,

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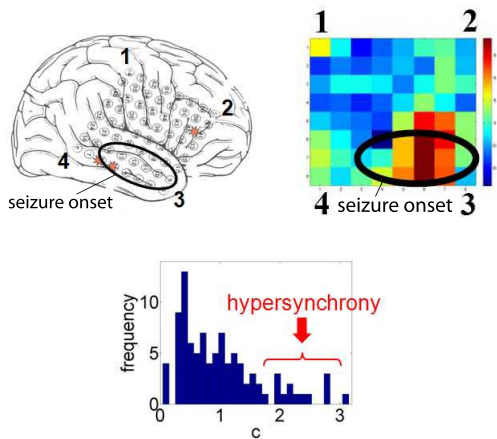
Fig. 1. Results for Patient 1 (grid electrodes): electrode placement (top left), local synchrony (local cross-correlation c; top right), histogram of local cross-correlation c (bottom). The ellipse depicts the seizure onset area, determined by trained electroencephalographers from seizure EEG (blinded to the results of this analysis).

Fig. 2. Results for Patient 2 and 3 (grid electrodes), from left to right: electrode placement and local cross-correlation c (top, Patient 2), electrode placement and local cross-correlation c (bottom, Patient 3).

and each EEG signal was then normalized (mean subtracted, divided by standard deviation). No further preprocessing was conducted; the channels were not selected based on any pre-existing knowledge, except that clearly dysfunctional data channels were discarded. We used a common reference for the data analysis. The reference electrode is in each case located far from the area of recording; it is very unlikely that the reference electrode would introduce spurious synchrony or eliminate actual synchrony between any regions.

We applied various univariate and multivariate measures to the EEG data, as will be detailed in the next sections. In order to compute those measures, we segmented the EEG signal in non-overlapping consecutive segments of 5s, in total 720 segments per 1-hour EEG signal. We computed all measures for each of those 5s segments. This allows us to investigate how the measures evolve over time, within the 1-hour EEG signals. By averaging over all 5s segments of a 1-hour EEG signal, we obtain average values of the statistical measures for that 1-hour EEG signal.

III. RESULTS

In the following, we describe the results obtained from analyzing the non-seizure intracranial EEG data (cf. Section II).

A. Regions of Relative Hypersynchrony

All patients showed distinct patterns of synchrony with certain subsets of channels, and therefore cortical regions, showing enhanced synchrony compared to other areas. Examples of such pattern are shown in Fig. 1 (Patient 1; grid electrodes), Fig. 2 (Patient 2 and 3; grid electrodes), Fig. 3 (Patient 4; grid electrodes), Fig. 4 (Patient 5; depth electrodes), and Fig. 5 (Patient 6; depth electrodes), in which local synchrony was each time calculated using the cross-correlation coefficient; we computed cross-correlations coefficients for 5s EEG segments, and averaged over all segments within a 1-hour EEG signal.
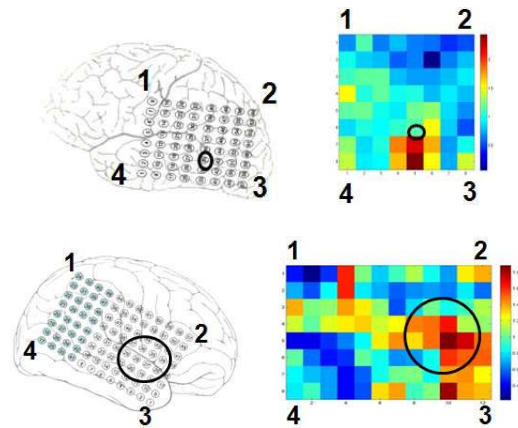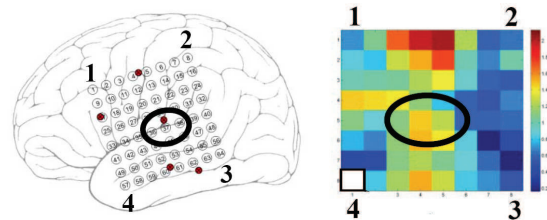

Fig. 3. Results for Patient 4 (grid electrodes): electrode placement (left), local synchrony (average cross-correlation c; right).
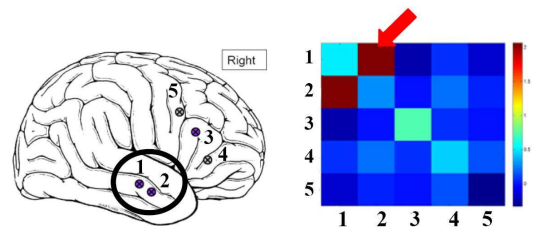

Fig. 4. Results for Patient 5 (depth electrodes): electrode placement (left), difference in pairwise synchrony between right and left hemisphere (right).
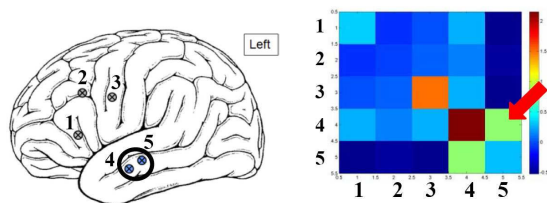

Fig. 5. Results for Patient 6 (depth electrodes): electrode placement (left), difference in pairwise synchrony between left and right hemisphere (right).
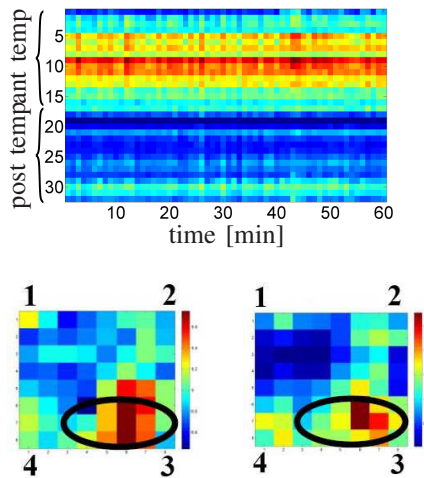
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Fig. 6. Results for Patient 1 (grid electrodes): evolution of local cross-correlation in temporal lobe over time (left), local coherence (middle), and local DTF (right).

In the case of grid electrodes (cf. Fig. 1 to 3), the local cross-correlation of an electrode is computed as the average pairwise cross-correlation of that electrode and its nearest neighbors. The local cross-correlation values are then normalized by the mean local cross-correlation, computed over all electrodes with the same neighborhood size: the 4 corners (neighborhood size 3), the other channels at the grid boundaries (size 5), and the inner channels (size 8). Without proper normalization, local synchrony values tend to be significantly larger at the grid boundaries. Fig. 1 shows a histogram of normalized local crosscorrelation values for Patient 1; there is one value for each of the electrodes in the 8×8 grid. One can see clear outliers in that histogram, they occur in the right anterior temporal lobe of Patient 1, as shown in Fig. 1 (top).

The cross-correlation between a pair of depth electrodes (cf. Fig. 4 and 5) is defined as the average cross-correlation between all pairs of channels from either electrode. For each hemisphere, we compute the synchrony of all pairs of depth electrodes; those values can be summarized in two symmetric 5×5 matrices of pairwise synchrony values, one for each hemisphere. Fig. 4 and 5 (right) show the difference between those pairwise-synchrony matrices; from those matrices it can be seen that the right (left) temporal lobe is hypersynchronous in Patient 5 (Patient 6).

B. Hypersynchrony is Stable over Time

The synchrony patterns seems to be stable over time. As an illustration, Fig. 6 (left) shows how local cross-correlation evolves in a 1-hour EEG segment of Patient 1; in particular, it shows cross-correlation values for each of the 5s segments of the 1-hour EEG signal. There was on average only 13% variance over the course of that 1-hour EEG segment. The same hypersynchrony patterns remained stable in other 1-hour EEG segments of the same patient, recorded on different days.

C. Hypersynchrony is Independent of Synchrony Measure

So far we have only considered the correlation coefficient as synchrony measure. We obtained very similar results using other synchrony methods, including phase synchrony [10], magnitude coherence [11], and Granger causality [12]; we considered 6 Granger measures in total, computed from multivariate autoregressive models (MVAR) of order 1 to 5. We applied the Granger measures separately to each electrode and its local neighborhood, since applying it to all electrodes simultaneously would involve a large number of MVAR parameters, which would be hard to estimate reliably from the short EEG segments. Results for coherence and directed transfer function (a Granger measure) for Patient 1 are shown in Fig. 6, middle and right respectively. Each method results in almost identical hypersynchronous areas.

D. Univariate Measures are Normal in Hypersynchronous Brain Areas

Besides synchrony measures, we also investigated signal power and several complexity measures: sample entropy [13], wavelet entropy [14] and approximate entropy [15].

The signal power (computed for 5s segments and then averaged over all segments of the 1-hour EEG signals) does not vary much over the grid, and it does not seem to be correlated with local synchrony (not shown here). In other words, hypersynchrony is not due to increased average power.

The three measures of complexity (sample entropy, wavelet entropy and approximate entropy) all lead to very similar results (not shown here). Moreover, they do not seem to be correlated with local synchrony. These observations seem to suggest that non-seizure hypersynchrony is a truly multivariate phenomenon: it reflects stronger coupling between multiple EEG signals. The average power and complexity of the EEG signals do not seem to be abnormal in hypersynchronous areas.

E. Hypersynchrony Correlates with Seizure Onset

And now the crucial question: where did the seizures start in the six patients considered in this study? The seizure onset areas, localized by trained electroencephalographers from seizure EEG (blinded to the results of this analysis), are depicted by ellipses in Fig. 1 to 5. In all patients except Patient 4, the seizure onset zone and hypersynchronous area overlap, there is strong correlation between both areas. Similar results have been obtained for grid electrodes (Patient 1–4) in earlier studies (e.g., [8]), but not for depth electrodes (Patient 5–6).

In Patient 4, there seems to be a substantial offset between the seizure onset zone (center of the grid) and hypersynchronous area (top of the grid); in earlier studies, such cases were considered as counterexamples. However, both areas were determined solely based on *grid* electrodes. In that patient, some *depth* electrodes also happened to be implanted. By analyzing those depth electrodes, it became clear that the seizures actually started in the hypersynchronous area at the
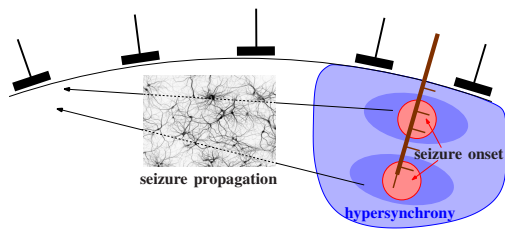
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Fig. 7. The seizures in Patient 4 actually started in the hypersynchronous area at the top of the grid, *deep inside* the brain, and then propagated towards the center of the grid to appear there at the surface

top of the grid, *deep inside* the brain, and then propagated towards the center of the grid to appear there at the surface (see Fig. 7). Moreover, the seizures started in the layers where hypersynchrony was the strongest; therefore, also in that patient there is strong correlation between seizure onset and hypersynchrony. In future studies, we will investigate the nature of this relation on a more fundamental basis.

IV. DISCUSSION

The case of Patient 4 illustrates an important point: grid electrodes alone may not suffice to correctly localize the seizure onset area; indeed, by analyzing *seizure* EEG at the grid electrodes alone, one would have wrongly localized the seizure onset area in the center of the grid. In contrast, the hypersynchronous area determined from *non-seizure* EEG at the grid electrodes coincided with the seizure onset area (top of the grid). However, hypersynchrony at the grid electrodes does not allow us to infer the depth at which seizures are generated; we obtained that information from depth electrodes.

More generally, since the number of implanted electrodes is limited (whether grid or depth), one cannot record the activity at every point in the brain; therefore, one cannot expect to always correctly identify the epileptic brain area through intracranial EEG recordings (whether grid and/or depth).

V. CONCLUSION

We have developed signal processing methods that use periods of intracranial non-seizure ("rest") EEG to localize seizure onset area. In contrast to most previous studies on seizure localization, we investigated non-seizure EEG: we analyzed EEG segments that are at least 48 hours separated from seizure activity. We found that certain areas of the cortex exhibit enhanced synchrony compared to other areas. The synchrony values seemed to be stable over time, and as a result, hypersynchronous areas may potentially be determined from short EEG recordings (1 to 10 min). We considered various multivariate (synchrony) measures, and have shown that they all lead to similar results; hypersynchrony is therefore well defined, and does not seem to be dependent on particular synchrony measures. Besides multivariate measures, we have also considered a variety of univariate measures. According to our analysis, the univariate measures do not correlate with hypersynchrony or seizure onset. However, we computed

those measures from 5s segments. As a result, our analysis does not directly take interictal spikes and other short events on the time scale of 0.1 to 1s into account; the effect of such events is probably lost in our analysis due to averaging. We also wish to point out that in the analysis of grid EEG data, we tried to avoid artifacts caused by boundary effects. Note that electrodes at the boundaries of the grid have fewer neighbors than electrodes in the interior of the grid; this difference in neighborhood size seems to bias the local synchrony values. Therefore, we normalized the (local) synchrony values depending on the location in the grid: electrodes at the corners in the grid, electrodes at the boundary of the grid (but not corners), and electrodes in the interior of the grid were all normalized separately.

The results of this paper (and related studies) may in the long term lead to more automated localization of the seizure focus, shorter semi-chronic invasive recordings and to greater utilization of short, intra-operative recordings. These same approaches may also be applied to non-invasive recordings from EEG and MEG. Ultimately, our understanding of the physiopathology of the epileptogenic zone will improve as will the safety and efficacy of our surgical management of medically refractory epilepsy.

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